

What is claimed is:

1. A method of identifying one or more nucleic acid molecules, comprising:

5 a) contacting at least one probe nucleic acid molecule with a survey population of nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate a probe-survey population mixture of nucleic acid molecules;

10 b) treating said probe-survey population mixture of nucleic acid molecules with a nucleolytic activity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

15 c) contacting said population of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acid molecules under conditions that promote hybridization between nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

20 d) identifying one or more of said attached nucleic acid molecules or one or more of said nucleolytic activity-protected nucleic acid molecules in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes.

25 2. The method of claim 1, further comprising exposing said population of nucleolytic activity-protected nucleic acid molecules to conditions that promote the formation of single-stranded nucleic acid molecules in the population of nucleolytic activity-protected nucleic acid molecules.

3. The method of claim 1, wherein said at least one probe nucleic acid molecule is at least partially single-stranded.

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4. The method of claim 1, wherein said at least one probe nucleic acid molecule comprises one or more nucleolytic activity-resistant linkages.

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5. The method of claim 1, wherein said at least one probe nucleic acid molecule comprises at least one detectable label.

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6. The method of claim 5, wherein said at least one detectable label comprises a radioisotope, a fluorochrome, or a specific binding member.

7. The method of claim 5, wherein said at least one detectable label does not comprise a mass-modified nucleotide.

8. The method of claim 1, wherein said at least one probe nucleic acid molecule is between 10 nucleotides and 100 nucleotides in length.

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9. The method of claim 1, wherein said at least one probe nucleic acid molecule comprises a known or suspected SNP or mutation.

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10. The method of claim 1, wherein said at least one probe nucleic acid comprises nucleic acid sequences that terminates at or adjacent to a known or suspected SNP or mutation.

11. The method of claim 1, wherein at least one of said at least one probe nucleic acid molecule is at least partially complementary or at least partially substantially complementary to at least one of said attached nucleic acid molecules.

12. The method of claim 1, wherein at least one of said at least one probe nucleic acid molecules has at least partially identical or at least partially substantially identical to at least one of said attached nucleic acid molecules.

13. The method of claim 1, wherein the survey population comprises RNA.

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14. The method of claim 1, wherein the survey population comprises DNA.

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15. The method of claim 1, wherein said at least one attached nucleic acid molecule is at least partially single-stranded.

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16. The method of claim 1, wherein said at least one attached nucleic acid molecule comprises at least one nucleolytic activity-resistant linkage.

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17. The method of claim 1, wherein said at least one attached nucleic acid molecule comprises at least one detectable label.

18. The method of claim 17, wherein said at least one detectable label comprises a radioisotope, a fluorochrome, or a specific binding member.

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19. The method of claim 1, wherein said at least one attached nucleic acid molecule is between 10 nucleotides and 100 nucleotides in length.

20. The method of claim 1, wherein said at least one attached nucleic acid molecule comprises a known or suspected SNP or mutation.

5 21. The method of claim 1, wherein said at least one attached nucleic acid comprises a nucleic acid sequences that terminates at or adjacent to a known or suspected SNP or mutation.

10 22. The method of claim 1, wherein at least one of said at least one attached nucleic acid molecules is at least partially complementary or at least partially substantially complementary to at least one of said probe nucleic acid molecules.

15 23. The method of claim 1, wherein at least one of said at least one attached nucleic acid molecules has at least partially identical or at least partially substantially identical to at least one of said probe nucleic acid molecules.

20 24. The method of claim 1, wherein said solid support is a DNA chip or array.

25 25. The method of claim 24, wherein said chip or array comprises nitrocellulose, nylon, silicon, glass, at least one plastic, at least one ceramic material, or at least one metal.

20 26. The method of claim 1, wherein said solid support comprises a particle or bead.

27. The method of claim 26, wherein said particle or bead is paramagnetic.

28. The method of claim 1, wherein said solid support is a dish or plate.

25 29. The method of claim 28, wherein said dish or plate comprises glass, polystyrene, polycarbonate, polyvinylchloride, or polypropylene.

30. The method of claim 1, wherein said solid support comprises a column matrix.

31. The method of claim 30, wherein said column matrix comprises agarose, cellulose, acrylamide, dextran, or magnetic particles.

32. The method of claim 1, wherein said nucleolytic activity comprises a nuclease.

33. The method of claim 32, wherein said nuclease is a single-strand specific nuclease.

34. The method of claim 33, wherein said single-strand specific nuclease is one or more of the group comprising mung bean nuclease, S1 nuclease, Rnase H, or Rnase T1.

35. The method of claim 1, further comprising amplifying nucleolytic activity-protected nucleic acid molecules.

36. The method of claim 35, wherein said amplification is substantially linear.

37. The method of claim 36, wherein said amplification uses DNA polymerase I, Klenow fragment, T.aquaticus polymerase, T4 DNA polymerase, SP6 RNA polymerase, or T7 RNA polymerase.

38. The method of claim 1, in which said identifying comprises labeling said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with at least one detectable label.

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39. The method of claim 38, in which said labeling of said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with said at least one detectable label uses at least one polymerase.

5 40. The method of claim 39, in which said at least one polymerase is one of the group comprising T4 DNA polymerase, T₄ aquaticus polymerase, Klenow fragment, DNA polymerase I, T7 RNA polymerase, SP6 RNA polymerase.

10 41. The method of claim 38, wherein said at least one detectable label comprises a radioisotope, a fluorochrome, an enzyme, or a specific binding member.

42. The method of claim 38, in which said at least one detectable label comprises at least one nucleotide.

43. The method of claim 38, wherein said at least one detectable label comprises at least two different nucleotides.

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✓ 44. A method of identifying one or more nucleic acid molecules, comprising:

a) contacting at least one probe nucleic acid molecule with a survey population of nucleic acid molecules to generate a mixture of nucleic acid molecules under conditions that promote hybridization between complementary nucleic acids;

b) treating said mixture of nucleic acid molecules with a nucleolytic activity, such that nucleolytic acitivity-sensitive nucleic acid molecules are digested, to generate a population of nucleolytic activity-protected nucleic acid molecules;

c) contacting said population of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acid molecules to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes;

d) treating said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes with a nucleolytic activity, such that nucleic acid molecules having single-stranded regions are cleaved; and

e) identifying one or more of said attached nucleic acids that remain bound to said solid support.

45. The method of claim 44, further comprising exposing said population of nucleolytic activity-protected nucleic acid molecules to conditions that promote the formation of single-stranded nucleic acid molecules in the population of nucleolytic activity-protected nucleic acid molecules.

46. The method of claim 44, wherein said at least one attached nucleic acid molecule comprises a detectable label.

5 47. The method of claim 46, wherein said detectable label comprises a radioisotope, a fluorochrome, an enzyme, or a specific binding member.

10 48. The method of claim 44, wherein said at least one attached nucleic acid molecule comprises a known or suspected SNP or mutation.

15 49. The method of claim 44, wherein said at least one probe nucleic acid molecule comprises sequences that terminate at or adjacent to a known or suspected SNP or mutation.

50. The method of claim 44, wherein said nucleolytic activity comprises a chemical or a nuclease.

51. The method of claim 50, wherein said nucleolytic activity comprises a nuclease.

52. The method of claim 51, wherein said nuclease is one of the group comprising Mung Bean nuclease S1 nuclease, RNase H, or RNase T1.

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✓ 53. A method of identifying one or more nucleic acid molecules, comprising:

5 a) contacting a first set of probe nucleic acid molecule with a first survey population of nucleic acid molecules to generate a first probe-survey population mixture of nucleic acid molecules under conditions that promote nucleic acid hybridization;

10 b) contacting a second set of probe nucleic acid molecules with a second survey population of nucleic acid molecules to generate a second probe-survey population mixture of nucleic acid molecules under conditions that promote nucleic acid hybridization;

15 c) treating said first and second mixtures of probe-survey population nucleic acid molecules with a nucleolytic activity, such that nucleolytic activity-sensitive nucleic acid molecules are digested, generating two populations of nucleolytic activity-protected nucleic acid molecules;

20 d) contacting said two populations of nucleolytic activity-protected nucleic acid molecules with a solid support comprising one or more attached nucleic acids to generate attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes; and

25 e) identifying one or more of said attached nucleic acids that are bound to one or more members of one or both of said two populations of nucleolytic activity-protected nucleic acids in one or more attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecule complexes.

54. The method of claim 53, further comprising exposing at least one of said two populations of nucleolytic activity-protected nucleic acid molecules to conditions that promote the formation of single-stranded nucleic acid molecules in the population of nucleolytic activity-protected nucleic acid molecules.

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55. The method of claim 53, wherein said first probe is labeled with at least one detectable label and said second probe is labeled with at least one detectable label.

10 56. The method of claim 53, wherein said first probe is labeled with a first detectable label and said second probe is labeled with a second detectable label, wherein said first detectable label and said second detectable label are different.

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57. The method of claim 1, further comprising contacting at least one signal nucleic acid molecule to said attached nucleic acid molecule/nucleolytic activity-protected nucleic acid molecules.

58. The method of claim 57, wherein said at least one signal nucleic acid molecule is at least partially single-stranded.

59. The method of claim 58, wherein said at least one signal nucleic acid molecule is at least partially complementary to at least one of said probe nucleic acid molecules.

25 60. The method of claim 57, wherein said at least one signal nucleic acid molecule is at least partially complementary to at least one nucleic acid molecule known to be or suspected of being in the survey population of nucleic acid molecules.

61. ~~The method of claim 57, wherein said at least signal nucleic acid molecule comprises at least one detectable label.~~

5 62. The method of claim 61, wherein said at least one detectable label comprises a radioisotope, a fluorochrome, or a specific binding member.

10 63. The method of claim 57, wherein said at least one signal nucleic acid molecule is between 10 nucleotides and 200 nucleotides in length.

15 64. A composition, comprising:

20 a) a solid support comprising a first population of at least two attached nucleic acid molecules immobilized thereon;

25 b) a second population of at least two nucleic acid molecules that are not bound to a solid support, wherein a majority of the members of said first population of attached nucleic acid molecules are at least partially complementary to one or more members of said second population of probe nucleic acid molecules.

30 65. The composition of claim 64, wherein the members of said first population of attached nucleic acids are at least partially single-stranded.

35 66. The composition of claim 64, wherein said members of said first population of attached nucleic acid molecules are between 10 nucleotides and 100 nucleotides in length.

67. The composition of claim 64, wherein said members of aid first population of attached nucleic acid molecules comprise a detectable label.

5 68. The composition of claim 64, wherein the members of said second population of nucleic acid molecules are at least partially single stranded.

10 69. The composition of claim 64, wherein said members of said second population of nucleic acid molecules are between 10 nucleotides and 100 nucleotides in length.

15 70. The composition of claim 64, wherein at least one of said members of said second population of nucleic acid molecules comprises a known or suspected SNP or mutation.

20 71. The composition of claim 64, wherein at least one of said members of said second population of nucleic acid molecules comprises nucleic acid sequences that terminate at or adjacent to a known or suspected SNP or mutation.

25 72. The composition of claim 64, further comprising a nuclease.

20 73. The composition of claim 72, wherein said nuclease is a single-strand specific nuclease.

25 74. The composition of claim 73, wherein said single-strand specific nuclease is a member of the group comprising S1 nuclease, Mung Bean nuclease, Rnase H, or RNase T1.

25 75. The composition of claim 64, further comprising a polymerase.

25 76. The composition of claim 75, wherein said polymerase is a member of the group comprising Klenow fragment, DNA polymerase I, T. aquaticus polymerase, or a reverse transcriptase.

77. The composition of claim 64, wherein the members of said second population of nucleic acid molecules comprise a detectable label.

78. The composition of claim 77, wherein said detectable label comprises a fluorochrome.

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79. The composition of claim 64, wherein the members of said first population of attached nucleic acids comprise a detectable label.

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80. The composition of claim 79, wherein said detectable label comprises a fluorochrome.

81. The composition of claim 64, further comprising buffers and reagents.